REMARKS/ARGUMENTS

Claims 1-14 remain in this application. Claims 10-12 have been withdrawn.

Claims 1-9 and 13-14 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which applicant regards as the invention. According to the Office action, the term "dissolution rate controlling polymer" is indefinite because any polymer would be reasonably expected to affect the dissolution rate and there is no clear definition in the specification as to what a "dissolution rate controlling polymer" actually is. Furthermore, according to the Office action, there is no indication as to "why the polymers recited in claim 5 are not dissolution rate controlling polymers. Office action, page 2. In response to applicant's arguments that the term "dissolution rate controlling polymer" is a term of art known to those of ordinary skill in the art, the Office failed to find this persuasive "as the specification gives no guidelines or criteria as to how a polymer would or would not qualify as a 'dissolution rate controlling polymer'." Office action, page 3. However, the fact that this term is a term of art known to those of ordinary skill in the art is exactly why a definition of the term is not required in the specification. An express definition of a term is not necessary if one of ordinary skill in the art understands the term as used in the context of the specification. See *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*, 309 F.3d 774, 780 (Fed. Cir. 2002). Dissolution rate controlling polymers are well known to those of ordinary skill in the art as high viscosity polymers widely used in the matrix tablet formulations to control release of an active ingredient.

The Office is also concerned that there is no explanation as to why the polymers recited in claim 5 are not considered "dissolution rate controlling polymers." The simple answer is that these polymers are described in the claim as being hydrophilic binders and, therefore, as one of ordinary skill in the art would immediately recognize, polymers used as binders are <u>not</u> the same as dissolution rate controlling polymers. Furthermore, as one of ordinary skill in the art would understand, several pharmaceutically acceptable polymers exhibit different functionalities depending on the molecular weight, viscosity, type and extend of substitution, etc. Hydroxypropyl methylcellulose or HPMC can be used as a coating agent, film former, binder,

viscosity-increasing agent or rate controlling polymer. A person of ordinary skill in the art can readily identify which specific types or grades of polymer are suitable for a particular purpose. Attached hereto marked as Exhibit A is a copy of pages 297-299 from the "Handbook of Pharmaceutical Excipients", IV Edition (2003), edited by R.C. Rowe, P.J. Sheskey and P.J. Weller, Pharmaceutical Press, London/Chicago. The enclosed excerpt describes the different uses for HPMC and the widespread variations in viscosity for various types of the polymer. Claim 5 of the pending application refers first to the polymer as being a hydrophilic binder and then sets forth a list of polymers that are suitable to be used as a binder. However, these polymers as set forth in claim 5 must first qualify as a binder to fall within the scope of claim 5. In other words, the claim is initially limited to hydrophilic binders and then further limited to the specific polymers set forth that must also be considered by one of ordinary skill in the art as being hydrophilic binders. It is not inconsistent for a specific subgroup of a broader polymeric class to be a hydrophilic binder and a different specific type of the same polymeric class to be a dissolution rate controlling polymer. By analogy, a claim reciting a red fruit could include an apple in the Markush group as could a claim reciting a green fruit. Apples could be set forth in the Markush groups of each claim and still be consistent with the broader description of the color fruit set forth in the claim. Each claim refers to an apple but in each case the apples are different colors. The same holds true for the polymers in the present case. HPMC can be a binder and it can also be a rate controlling polymer.

In the Office action, the Examiner asks why the polymers in claims 1 and 5 do not affect the rate of dissolution in a composition. As described above, the reason is because these polymers have different characteristics in each situation. One of ordinary skill in the art would never consider polyvinylpyrrolidone used as a binder as being a rate controlling polymer. The Office is reminded that the terms of the claim must be construed as one of ordinary skill in the art would construe the claims and such a stretched reading of the claims to include any polymer that would have any effect however small on the dissolution rate as being a dissolution rate controlling polymer is inconsistent with the proper construction of the claims. Therefore, applicants respectfully submit that the term "dissolution rate controlling polymer" is not indefinite, but instead is a well established and commonly understood meaning known to those of ordinary skill in the art. Accordingly, applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

Claims 1-9 and 13-14 stand rejected as being anticipated by or obvious over Rampal et al. (WO 03/017981). However, applicants submit that the claims once properly construed to afford weight to the dissolution rate controlling polymer are novel and non-obvious over the cited references. Rampal et al. clearly disclose the use of dissolution rate controlling polymers in the disclosed dosage forms. The claims of the present application, by contrast, refer to a dosage form that does not contain a dissolution rate controlling polymer. Once this limitation is afforded the proper weight in evaluating the patentability of the claims, these claims clearly distinguish over the disclosure in Rampal et al. Therefore, since Rampal et al. failed to disclose or suggest a dosage form that does not contain a dissolution rate controlling polymer, there can be no anticipation. Therefore, applicants respectfully request that the rejection be withdrawn.

In view of the foregoing, it is respectfully submitted that all of the pending claims are in condition for allowance and favorable action on the merits is requested. Any questions concerning this application may be directed to applicant's undersigned attorney at the telephone number indicated below.

Respectfully submitted,

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Exhibit A

Handbook of Pharmaceutical Excipients

Fourth Edition

Edited by
Raymond C Rowe, Paul J Sheskey
and Paul J Weller

Pharmaceutical Press

APhA
American Pharmaceutical Association

Hypromellose

1 Nonproprietary Names

BP: Hypromellose
JP: Hydroxypropylmethylcellulose
PhEur: Hypromellosum
USP: Hypromellose

2 Synonyms

Benecel MHPC; cellulose, hydroxypropyl methyl ether; E464; hydroxypropyl methylcellulose; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Pharmacoat*; *Spectracel 6*; *Spectracel 15*; *Tylopur*.

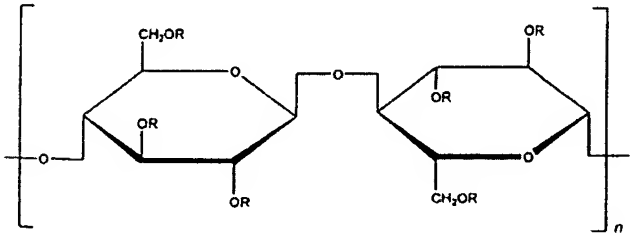
3 Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl methyl ether [9004-65-3]

4 Empirical Formula Molecular Weight

The PhEur 2002 describes hypromellose as a partly O-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20°C. Hypromellose defined in the USP 25 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g., hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH_3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group ($OCH_2CH(OH)CH_3$), calculated on a dried basis. Molecular weight is approximately 10 000–1 500 000. The JP 2001 includes three separate monographs for hypromellose: hydroxypropylmethylcellulose 2208, 2906, and 2910, respectively.

5 Structural Formula



where R is H, CH_3, or $CH_3CH(OH)CH_2$

6 Functional Category

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral and topical pharmaceutical formulations.

In oral products, hypromellose is primarily used as a tablet binder,[1] in film-coating,[2–7] and as an extended-release tablet matrix.[8–12] Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules.

Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

Hypromellose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Compared with methylcellulose, hypromellose produces solutions of greater clarity, with fewer undispersed fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions.

Hypromellose is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments.

In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

8 Description

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

9 Pharmacopeial Specifications

See Table I.

10 Typical Properties

Acidity/alkalinity: pH = 5.5–8.0 for a 1% w/w aqueous solution.
Ash: 1.5–3.0%, depending upon the grade.
Autoignition temperature: 360°C
Density (bulk): 0.341 g/cm^3
Density (tapped): 0.557 g/cm^3
Density (true): 1.326 g/cm^3
Melting point: browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.
Moisture content: hypromellose absorbs moisture from the atmosphere, the amount of water absorbed depending upon the initial moisture content and the temperature and relative humidity of the surrounding air. *See* Figure 1.

Table II: Typical viscosity values for 2% (w/v) aqueous solutions of *Methocel* (Dow Chemical Co.). Viscosities measured at 20°C.

Methocel grade	Nominal	Viscosity (mPa s)
K100LVP	100	80–120
K4M	4000	3000–5600
K15MP	15000	12000–21000
K100MP	100000	80000–120000
E4MP	4000	3500–5600
E10MP CR	10000	8000–13000
E3 PREM.LV	–	2.4–3.6
E5 PREM.LV	–	4–6
E6 PREM.LV	–	5–7
E15 PREM.LV	–	12–18
E50 PREM.LV	–	40–60
K3 PREM.LV	–	2.4–3.6

To prepare an aqueous solution, it is recommended that hypromellose is dispersed and thoroughly hydrated in about 20–30% of the required amount of water. The water should be vigorously stirred and heated to 80–90°C, then the remaining hypromellose added. Cold water should then be added to produce the required volume.

When a water-miscible organic solvent such as ethanol, glycol, or mixtures of ethanol and dichloromethane is used, the hypromellose should first be dispersed into the organic solvent, at a ratio of 5–8 parts of solvent to 1 part of hypromellose. Cold water is then added to produce the required volume.

11 Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying.

Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gel point is 50–90°C, depending upon the grade and concentration of material.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.[13] However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking.

Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

2 Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

3 Method of Manufacture

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

14 Safety

Hypromellose is widely used as an excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.[14] The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health.[15]

LD_{50} (mouse, IP): 5 g/kg[16]
LD_{50} (rat, IP): 5.2 g/kg

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritant to the eyes and eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

16 Regulatory Status

GRAS listed. Accepted as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (ophthalmic preparations; oral capsules, suspensions, syrups, and tablets; topical and vaginal preparations). Included in nonparenteral medicines licensed in the UK.

17 Related Substances

Hydroxyethyl cellulose; hydroxypropyl cellulose; hypromellose phthalate; methylcellulose.

18 Comments

Powdered or granular, surface-treated grades of hypromellose are also available that are dispersible in cold water. These are not recommended for oral use.

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21 Author

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22 Date of Revision

25 October 2002.